(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 May 2001 (10.05.2001)

PCT

(10) International Publication Number
WO 01/32646 A2

(51) International Patent Classification[7]: C07D 401/00

(21) International Application Number: PCT/EP00/10911

(22) International Filing Date:
2 November 2000 (02.11.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9926302.2 5 November 1999 (05.11.1999) GB

(71) Applicant *(for all designated States except US)*: **SMITHKLINE BEECHAM P.L.C.** [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BROMIDGE, Steven, Mark** [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **SERAFINOWSKA, Halina, Teresa** [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: **WATERS, David, Martin**; SmithKline Beecham, Corporate Intellectual Property, Two Horizons Court, Brentford, Middlesex TW8 9BD (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/32646 A2

(54) Title: NOVEL COMPOUNDS

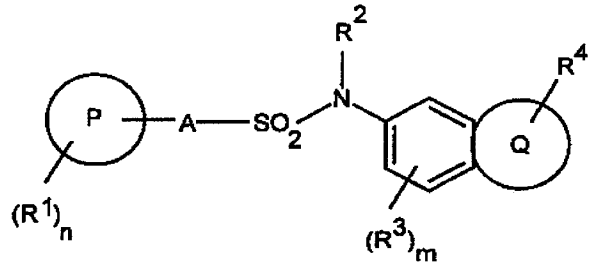
(57) Abstract: Novel sulfonamide compounds having CNS activity, processes for their preparation, to compositions containing the same and their use as medicaments.

NOVEL COMPOUNDS

This invention relates to novel sulfonamide compounds having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS disorders.

WO 98/27081, WO 99/37623 and WO 99/42465 disclose sulfonamide compounds that possess 5-HT_6 receptor antagonist activity and which are claimed to be useful in the treatment of various CNS disorders. WO 94/21619 and EP 0701819 both disclose a series of naphthalene derivatives that are claimed to be 5-HT_{1A} receptor ligands.

A structurally distinct class of compounds has now been found that also exhibit 5-HT_6 receptor antagonist activity. The present invention therefore provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein

P is phenyl, naphthyl, a 5 or 6 membered heteroaryl ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, or a bicyclic or tricyclic heteroaryl ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur;

A is a single bond, a C_{1-6}alkylene or a C_{2-6}alkenylene group;

R^1 is halogen, C_{1-6}alkyl optionally substituted by one or more halogen atoms, C_{3-6}cycloalkyl, phenyl, COC_{1-6}alkyl, C_{1-6}alkoxy, OCF_3, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, nitro, amino, C_{1-6}alkylamino or diC_{1-6}alkylamino;

n is 0, 1, 2, 3, 4 or 5;

R^2 is hydrogen, C_{1-6}alkyl or together with a group R^3 forms a group -(CR^6R^7)p- where R^6 and R^7 are independently hydrogen or C_{1-6}alkyl and p is 2, 3 or 4;

R^3 is C_{1-6}alkyl optionally substituted by one or more halogen atoms, halogen, C_{1-6}alkoxy or together with the group R^2 forms a group -(CR^6R^7)p- as defined above;

m is 0, 1 or 2;

R^4 is a group -X-R^5 where X is a single bond, CH_2, O, NH or N-C_{1-6}alkyl and R^5 is an optionally substituted 5- to 7-membered heterocyclic ring or a bicyclic heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen;
Q is a phenyl ring or is a 6 membered heteroaryl ring containing one or two nitrogen atoms.

C_{1-6}alkyl groups, whether alone or as part of another group, may be straight chain or branched. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

When P is naphthyl this is intended to denote both naphth-1-yl and naphth-2-yl groups. When P is a 5 or 6-membered heteroaryl ring suitable examples include thienyl, furyl, pyrrolyl, triazolyl, diazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyridyl, pyrimidyl and pyrazinyl. When P is a bicyclic heteroaryl ring suitable examples include indolyl, benzofuryl, benzothienyl, quinolinyl and isoquinolinyl. When P is a tricyclic heteroaryl ring a preferred example is dibenzofuryl. The heteroaryl rings can be linked to the remainder of the molecule via any suitable carbon atom or, when present, a nitrogen atom.

Preferably P is phenyl, naphthyl, benzofuryl or benzothienyl.

Preferably A is a single bond, a methylene or ethylene group or a -CH=CH- group. Most preferably A is a single bond.

When n is more than 1 the groups R^1 can be the same or different. Preferably R^1 is halogen (particular chloro or bromo), or a C_{1-6}alkyl group optionally substituted by one or more halogen atoms, for example, methyl, ethyl, isopropyl, t-butyl or trifluoromethyl.

Preferably n is 0, 1, 2 or 3, particularly 1 or 2.

When R^2 together with a group R^3 forms a further group -(CR^6R^7)p- both of the groups R^6 and R^7 are preferably hydrogen and p is preferably 2. R^2 is preferably hydrogen.

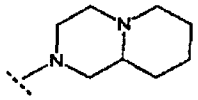
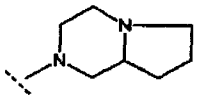
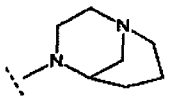
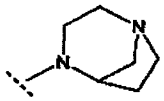
A substituent R^3 can be attached at any unsubstituted carbon atom within the fused ring. When m is more than 1 the groups R^3 can be the same or different. It will be appreciated that when the R^2/R^3 groups are linked together, the group R^3 must be attached to one of the carbon atoms of the fused ring with an ortho relationship with respect to the sulfonamide linkage. Preferably m is 0.

The group R^4 can be attached at any unsubstituted carbon atom within the ring Q.

When R^5 is a 5- to 7- membered heterocyclic ring suitable examples include piperazinyl, piperidinyl, pyrrolidinyl and morpholinyl. The 5- to 7- membered heterocyclic rings can be linked to the remainder of the molecule via a carbon atom or, when present, a suitable nitrogen atom. It will be appreciated however, that when X is O,

NH or N-C_{1-6}alkyl then the 5- to 7- membered heterocyclic ring must be linked to the rest of the molecule via a carbon atom. Preferably X is a single bond (i.e. $R^4 = R^5$) and the 5- to 7-membered heterocyclic ring is attached to the rest of the molecule via a suitable nitrogen atom.

When R^5 is a bicyclic heterocyclic ring, X is preferably a single bond (i.e. $R^4 = R^5$) and suitable examples of such groups are

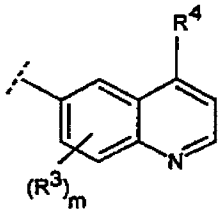



and


Optional substituents for rings within the definition of R^5, which can be present on carbon and/or nitrogen atoms, include C_{1-6}alkyl, in particular methyl.

Most preferably R^4 is an unsubstituted piperazine or N-methyl piperazine attached to the rest of the molecule via a suitable nitrogen atom.

Suitably Q is a phenyl ring or is a 6 membered heteroaryl ring containing one or two nitrogen atoms. Preferably Q, together with the phenyl ring to which it is fused, forms a quinoline, isoquinoline or quinazoline ring.

Most preferably Q, together with the phenyl ring to which it is fused, forms a quinoline ring, and the substituent R^4 is at the 4 -position, that is to say, a group of formula (A)



(A)

Particular preferred compounds of this invention include:

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-[4-methylpiperazin-1-yl]-quinolin-6-yl)-amide,

5-Chloro-naphthalene-2-sulfonic acid (4-[4-methyl-piperazin-1-yl]-quinolin-6-yl)-amide,

4-Bromo-*N*-[4-(4-methyl-piperazin-1-yl)-quinolin-6-yl]-benzenesulfonamide,

3,5-Dichloro-*N*-[4-(4-methyl-piperazin-1-yl)-quinolin-6-yl]-benzenesulfonamide,

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-[3,5-dimethylpiperazin-1-yl]-quinolin-6-yl)-amide,

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid [4-(4-methyl-piperazin-6-yl]-quinazolin-6-yl)amide,

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)-amide,

3,5-Dichloro-*N*-(4-piperazin-1-yl-quinolin-6-yl)-benzenesulfonamide,
5-Chloro-3-methyl-benzofuran-2-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)amide,
5,7-Dichloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)-amide,
5-Chloro-naphthalene-2-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)-amide,
5-Chloro-naphthalene-1-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)-amide,
5-Chloro-2-methyl-benzo[b]thiophene-3-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)-amide,
2-Dibenzofuran-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)-amide,
5-Chloro-3,7-dimethyl-benzo[b]thiophene-2-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)-amide,
7-Chloro-2-methyl-benzo[b]thiophene-3-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)-amide,
4,6-Dichloro-2-methyl-benzo[b]thiophene-3-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)-amide,
5,7-Dichloro-2-methyl-benzo[b]thiophene-3-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)-amide,
Biphenyl-4-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)-amide,
4-*tert*-Butyl-*N*-(4-piperazin-1-yl-quinolin-6-yl)-benzenesulfonamide,
5-Bromo-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)-amide,
4-*n*-Butyl-*N*-(4-piperazin-1-yl-quinolin-6-yl)-benzenesulfonamide,
4-Chloro-2,5-dimethyl-*N*-(4-piperazin-1-yl-quinolin-6-yl)-benzenesulfonamide,
5-Chloro-3-ethyl-benzo[b]thiophene-2-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)-amide,
5-Chloro-3-isopropyl-benzo[b]thiophene-2-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)-amide,
4-Iodo-*N*-(4-piperazin-1-yl-quinolin-6-yl)-benzenesulfonamide,
1-(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-8-(4-methyl-piperazin-1-yl)-2,3-dihydro-1*H*-pyrrolo[2,3-g]quinoline,
5-Chloro-naphthalene-2-sulfonic acid (2-methyl-4-piperazin-1-yl-quinolin-6-yl) amide,
5-Chloro-3-methyl-benzo[b]thiophen-2-sulfonic acid (2-methyl-4-piperazin-1-yl-quinolin-6-yl) amide,
5-Chloro-3-methyl-benzofuran-2-sulfonic acid (2-methyl-4-piperazin-1-yl-quinolin-6-yl) amide,
5-Chloro-naphthalene-2-sulfonic acid (3-methyl-4-piperazin-1-yl-quinolin-6-yl) amide,
5-Chloro-3-methyl-benzo[b]thiophen-2-sulfonic acid (3-methyl-4-piperazin-1-yl-quinolin-6-yl) amide,
5,7-Dichloro-3-methyl-benzo[b]thiophen-2-sulfonic acid (3-methyl-4-piperazin-1-yl-quinolin-6-yl) amide,

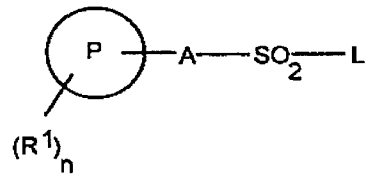
5-Chloro-3-methyl-benzofuran-2-sulfonic acid (3-methyl-4-piperazin-1-yl-quinolin-6-yl) amide,
4-*tert*-Butyl-*N*-[4-(S-hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-quinolin-6-yl-benzene sulfonamide,
5-Chloro-3-methyl-benzo[b]thiophen-2-sulfonic acid [4-(S-hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-quinolin-6-yl] amide,
5-Chloro-2-methyl-benzo[b]thiophene-3-sulfonic acid (4-[3,5-dimethylpiperazin-1-yl]-quinolin-6-yl)-amide,
5-Chloro-3-methyl-benzo[b]thiophene-2-sulphonic acid [4-((S)-3-methyl-piperazine-1yl)-quinolin-6-yl]-amide,
5-Chloro-3-methyl-benzo[b]thiophene-2-sulphonic acid [4-((R)-3-methyl-piperazine-1-yl)-quinolin-6-yl]-amide,
5-Chloro-3-methyl-benzo[b]thiophene-2-sulphonic acid [4-((R)-3-isopropyl-piperazine-1-yl)-quinolin-6-yl]-amide,
5-Chloro-3-methyl-benzo[b]thiophene-2-sulphonic acid [4-(*trans*-2,5-di-methyl-piperazine-1-yl)-quinolin-6-yl]-amide,
5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid [8-(4-methyl-piperazin-1-yl)-naphthalen-2-yl]-amide
or a pharmaceutically acceptable salt thereof.

The compounds of the formula (I) can form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulphonic.

Compounds of formula (I) may also form solvates such as hydrates, and the invention also extends to these forms. When referred to herein, it is understood that the term 'compound of formula (I)' also includes these forms.

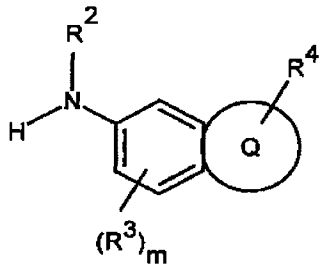
Certain compounds of formula (I) are capable of existing in stereoisomeric forms including diastereomers and enantiomers and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises the coupling of a compound of formula (II) or protected derivatives thereof:



(II)

in which R^1, n, P and A are as defined in formula (I) and L is a leaving group with a compound of formula (III) or protected derivatives thereof;



(III)

in which Q, m, R^2, R^3 and R^4 are as defined in formula (I) and optionally thereafter:

- removing any protecting groups,
- forming a pharmaceutically acceptable salt.

Suitable leaving groups include halogen, in particular chloro. The reaction of a compounds of formulae (II) and (III) is carried out by mixing the two reagents together, optionally in an inert solvent such as dichloromethane or acetone. Such a reaction may be carried out in the presence of base.

Those skilled in the art will appreciate that it may be necessary to protect certain groups. Suitable protecting groups and methods for their attachment and removal are conventional in the art of organic chemistry, such as those described in Greene T.W. 'Protective groups in organic synthesis' New York, Wiley (1981). For example, suitable protecting groups for the piperazine group include BOC, $COCCl_3$, $COCF_3$ and methyl the latter of which may be removed by treatment with 1-chloroethyl chloroformate according to standard procedures.

N-substituted piperazines can be prepared by acylation or alkylation of the appropriate NH-piperazine compound according to standard procedures.

Compounds of formulae (II) and (III) are commercially available, may be prepared according to methods described herein, by known methods or by analogous methods thereto.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

Compounds of formula (I) and their pharmaceutically acceptable salts have 5-HT_6 receptor antagonist activity and are believed to be of potential use in the treatment of certain CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, cognitive memory disorders (e.g. age related cognitive decline and/or Alzheimers disease), Parkinson's Disease, ADHD (attention deficit / hyperactivity disorder), sleep disorders (including disturbances of circadian rhythm), feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the treatment of certain GI (gastrointestinal) disorders such as IBS (Irritable Bowel Syndrome).

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of the above disorders.

In particular the invention provides a compound of general formula (I) or a pharmaceutically acceptable salt for use in the treatment or prophylaxis of schizophrenia, ADHD, cognitive memory enhancement, anxiety and/or depression.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a safe and therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis of the above disorders.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusable solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid

preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 20.0 mg, for example 0.2 to 5 mg; and such unit doses may be administered more than once a day, for example two or three a day, so that the total daily dosage is in the range of about 0.5 to 100 mg; and such therapy may extend for a number of weeks or months.

When administered in accordance with the invention, no unacceptable toxicological effects are expected with the compounds of the invention.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1

6-Nitroquinoline-1-oxide (D1)

A solution of *m*-chloroperoxybenzoic acid (57-86%, 37.5g) in dichloromethane (800ml) was added over 1.5 hours to a stirred, ice-cooled solution of 6-nitroquinoline (25g, 0.14mmol) in dichloromethane (500ml). The mixture was warmed to room temperature, stirred for a further 18 hours and then washed with 5% sodium metabisulfite (1l), saturated K_2CO_3 solution (1l), dried (Na_2SO_4), filtered and the filtrate concentrated *in vacuo* to give the title compound (D1) as a yellow solid (25g, 91%), MH^+ 191.

Description 2

4-Chloro-6-nitroquinoline (D2)

6-Nitroquinoline-1-oxide (24.5g, 0.13mmol) was added portionwise to ice-cooled , stirred phosphorus oxychloride (150ml). The mixture was then heated to reflux under argon for 3 hours to produce a precipitate. After cooling the mixture to room temperature, it was slowly poured onto stirred ice (1.5Kg) then with maintained cooling it was neutralised with 40% NaOH solution, resulting in a solid precipitating which was filtered and washed with water (6 x 200ml). The solid was dried at 60°C under vacuum to afford crude material which was purified by column chromatography over silica gel eluting with dichloromethane to give the following isomeric compounds:

4-Chloro-6-nitroquinoline (D2): yellow solid (12.0g, 45%), MH^+ 209/211,
3-Chloro-6-nitroquinoline: white solid (2.6g, 10%), MH^+ 209/211,
2-Chloro-6-nitroquinoline: yellow solid (1.4g, 5%), MH^+ 209/211,

Description 3

4-(4-Methylpiperazin-1-yl)-6-nitroquinoline (D3)

A solution of 4-chloro-6-nitroquinoline (D2) (3.0g, 14.4mmol) in N-methylpiperazine (30ml) was stirred at 60°C for 24 hours under argon. The solution was concentrated *in vacuo* to an oil which was dissolved in dichloromethane (100ml) and the solution was washed with water (3 x 100ml). The organic phase was dried (Na_2SO_4) and concentrated to give the title compound (D3) as a yellow solid (3.8g, 97%), MH^+ 273.

Description 4

6-Amino-4-(4-methylpiperazin-1-yl)quinoline (D4)

A suspension of 5% Pd/C (0.3g) in a solution of 4-(4-methylpiperazin-1-yl)-6-nitroquinoline (D3) (3.8g, 14.0mmol) in ethanol (100ml) was stirred in an atmosphere of hydrogen for 24 hours. The mixture was filtered and the filtrate concentrated *in vacuo* to give the title compound (D4) as a solid (3.3.g, 97%), MH^+ 243.

Description 5

6-Nitro-4-(piperazin-1-yl)quinoline (D5)

A solution of 4-chloro-6-nitroquinoline (D2) (5.0g, 24.0mmol) and piperazine (8.3g, 96mmol) in toluene (100ml) was heated to reflux for 24 hours under argon. The solution was concentrated *in vacuo* and the residue was dissolved in dichloromethane (150ml) washed with water (3 x 200ml), dried (Na_2SO_4) and concentrated to give the title compound (D5) as an orange solid (6.0g, 98%), MH^+259.

Description 6

4-(4-*tert*-Butoxycarbonylpiperazin-1-yl)-6-nitroquinoline (D6)

Water (80ml) was added over 5 min to a stirred solution of 6-Nitro-4-(piperazin-1-yl)quinoline (D5) (6.0g, 23.4mmol) in tetrahydrofuran (80ml) at room temperature. To this solution was added a solution of di-*tert*-butyldicarbonate (5.1g, 23.4mmol) in tetrahydrofuran (20ml) over 0.5 hours followed by the portion-wise addition of potassium carbonate (3.4g, 24.6mmol). The mixture was stirred for 3 days and then the organic solvent was evaporated *in vacuo* and the remaining aqueous residue was extracted with dichloromethane (4 x 150ml). The extract was dried (Na_2SO_4) and concentrated to an oil which crystallised in diethyl ether/hexane (1:1) to give the title compound (D6) (7.7g, 92%), MH^+ 359.

Description 7

6-Amino-4-(4- *tert*-butoxycarbonylpiperazin-1-yl)quinoline (D7)

4-(4-*tert*-Butoxycarbonylpiperazin-1-yl)-6-nitroquinoline (D6) (7.7g, 21.5mmol) was hydrogenated as described in Description 4 to give the title compound (D7) as a yellow solid (7.1g, 100%), MH^+ 329.

Description 8

1-Benzyl-5-nitroindoline (D8)

To a stirred solution of 5-nitroindoline (50g, 0.30mol) in acetone (500ml) was added anhydrous potassium carbonate (55.3g, 0.40mol) followed by dropwise addition of benzyl bromide (42ml, 0.35mol) over 45 minutes. The mixture was stirred at room temp for 24 hours. Further benzyl bromide (10.0ml, 0.08mol) and potassium carbonate (12.0g, 0.09mol) were added and the mixture heated at reflux for 3 days. On cooling the mixture was filtered and the filtrate evaporated *in vacuo* to a dark red oil. Trituration of the oil with hexane afforded the title compound (D8) as an orange crystalline solid (79.0g, 100%)

^1H NMR (250MHz,$CDCl_3$) δ (ppm): 8.05 (d, 1H), 7.91 (s, 1H), 7.25-7.40 (m, 5H), 6.35 (d, 1H), 4.35 (s, 2H), 3.63 (t, 2H), 3.09 (t, 2H). MS: m/z = 255 (MH^+)

Description 9

5-Amino-1-benzyl indoline (D9)

A mixture of 1-benzyl-5-nitroindoline (Description 8; 20.0g, 0.08mol), tin(II)chloride (60.0g, 0.32mol) and concentrated HCl (40ml) in methanol (400ml) was heated at reflux for 16 hours. On cooling the mixture was evaporated *in vacuo* to a red oil which was partitioned between CH_2Cl_2 and water, basified with 40% NaOH solution and the insoluble tin residues removed by filtration. The filtrate was extracted with CH_2Cl_2 (2x), dried (Na_2SO_4) and evaporated *in vacuo* to afford the title compound (D9) as a dark green oil (10.5g, 60%).

^1H NMR (250MHz,$CDCl_3$) δ (ppm): 7.23-7.41(m, 5H), 6.58 (s, 1H), 6.45 (dd, 1H), 6.37 (d, 1H), 4.13 (s, 2H), 3.31 (br s, 2H), 3.18 (t, 2H), 2.87 (t, 2H). MS: m/z = 225 (MH^+)

Description 10

Diethyl(1-benzylindolin-5-yl-amino)methylene malonate (D10)

Diethylethoxymethylene malonate (9.45ml, 0.05 mol) was added to a solution of 5-amino-1-benzyl indoline (Description 9; 10.5g, 0.05mol) in toluene (500ml) and the mixture heated at reflux under argon for 1.5 hours. On cooling the solvent was removed *in vacuo* to give a brown oil 19.6g. Purification of the oil by flash chromatography (eluent Hexane:EtOAc 70:30) afforded the title compound (D10) as a yellow crystalline solid (14.3g, 77%).

^{1}H NMR (250MHz,$CDCl_3$) δ (ppm): 8.42 (d, 1H), 7.28-7.38 (m, 5H), 6.93 (s, 1H), 6.83 (dd, 1H), 6.44 (d, 2H), 4.17-4.33 (m, 6H), 3.36 (t, 2H), 2.99 (t, 2H), 1.25-1.40 (m, 6H). NH not observed. MS: m/z = 395 (MH^+)

Description 11

Ethyl 1-benzyl-8-chloro-2,3-dihydropyrrolo[2,3-g]quinoline-7-carboxylate (D11)

Diethyl(1-benzylindolin-5-yl-amino)methylene malonate (Description 10; 10.0g, 25.3mmol) in phosphorus oxychloride (40ml) was heated at reflux under argon for 2.5 hours. The mixture was reduced *in vacuo* and the residual oil treated with 10% Na_2CO_3 solution until basic. Extraction with CH_2Cl_2 afforded a red gum which was purified using column chromatography (eluent Hexane:EtOAc 70:30) to afford the title compound (D11) as a yellow crystalline solid (6.3g, 68%).

^{1}H NMR (250MHz,$CDCl_3$) δ (ppm): 8.81 (s, 1H), 7.69 (s, 1H), 7.27-7.40 (m, 5H), 7.02 (s, 1H), 4.51 (s, 2H), 4.46 (q, 2H), 3.59 (t, 2H), 3.24 (t, 2H), 1.44 (t, 3H). MS: m/z = 367 (MH^+)

Description 12

Ethyl 1-benzyl-8-(4-methyl-1-piperazinyl)-2,3-dihydropyrrolo-[2,3-g]quinoline-7-carboxylate (D12)

To a mixture of ethyl 1-benzyl-8-chloro-2,3-dihydropyrrolo[2,3-g]quinoline-7-carboxylate (Description 11; 5.5g, 15.0mmol) and N-methylpiperazine (5.0ml, 45.0mmol) in DMF (50ml) was added triethylamine (6.3ml, 45.0mmol) and the mixture heated at 90°C under argon for 16 hours. The DMF was removed *in vacuo* and the residue partitioned between CH_2Cl_2 and water. The organics were separated and the aqueous further extracted with CH_2Cl_2 (1x). The combined organics were dried (Na_2SO_4) and evaporated *in vacuo* to an orange oil which was triturated with ethyl acetate (x2) to give the title compound (D12) as a yellow solid (4.83g, 75%).

^{1}H NMR (250MHz,$CDCl_3$) δ (ppm): 8.54 (s, 1H), 7.67 (s, 1H), 7.29-7.41 (m, 5H), 6.76 (s, 1H), 4.45 (s, 2H), 4.41 (q, 2H), 3.60 (t, 2H), 3.17-3.25 (m, 6H), 2.40 (br s, 4H), 2.30 (s, 3H), 1.40 (t, 3H). MS: m/z = 431 (MH^+)

Description 13

1-Benzyl-8-(4-methyl-1-piperazinyl)-2,3-dihydropyrrolo-[2,3-g]quinoline-7-carboxylate (D13)

Ethyl 1-benzyl-8-(4-methyl-1-piperazinyl)-2,3-dihydropyrrolo-[2,3-g]quinoline-7-carboxylate (Description 12; 4.8g, 11.1mmol) in ethanol (100ml) was treated with a solution of sodium hydroxide (0.89g, 22.2mmol) in water (20ml) and the mixture heated at reflux under argon for 16 hours. The ethanol was removed *in vacuo*, the residue diluted with water and treated with 1M HCl solution (pH 7). A yellow precipitate was filtered off, dried in a vacuum oven, identified as the title compound (D13, 4.5g, 100%).

^{1}H NMR (250MHz,d_6DMSO) δ (ppm): 8.35 (s, 1H), 7.56 (s, 1H), 7.39-7.55 (m, 5H), 6.73 (s, 1H), 4.50 (s, 2H), 3.56 (t, 2H), 3.34 (br s, 4H), 3.16 (t, 2H), 2.87 (br s, 4H), 2.61 (s, 3H). OH not observed. MS: m/z = 403 (MH^+).

Description 14

1-Benzyl-8-(4-methyl-1-piperazinyl)-2,3-dihydropyrrolo-[2,3-g]quinoline (D14)

1-Benzyl-8-(4-methyl-1-piperazinyl)-2,3-dihydropyrrolo-[2,3-g]quinoline-7-carboxylate (Description 13; 4.46g, 11.1mmol) was added in small portions with care (down an air condenser) to diphenyl ether (100ml) at 250°C over 15 minutes. The mixture was heated at 250-270°C for a further 10 minutes and allowed to cool to 35°C. The solution was then poured into hexane (200ml) and extracted into 2M HCl solution. The acidic extracts were washed with hexane (4x) to remove the diphenyl ether and basified with 10% Na_2CO_3 solution. Extraction with ethyl acetate (3x) gave the title compound (D14) as a yellow crystalline solid (4.0g, 100%).

^{1}H NMR (250MHz, $CDCl_3$) δ (ppm): 8.42 (d, 1H), 7.68 (s, 1H), 7.28-7.42 (m, 5H), 6.73 (d, 1H), 6.61 (s, 1H), 4.42 (s, 2H), 3.57 (t, 2H), 3.20 (t, 2H), 3.08 (br s, 4H), 2.42 (br s, 4H), 2.36 (s, 3H). MS: m/z = 359 (MH^+).

Description 15

8-(4-Methyl-1-piperazinyl)-2,3-dihydropyrrolo-[2,3-g]quinoline (D15)

1-Benzyl-8-(4-methyl-1-piperazinyl)-2,3-dihydropyrrolo-[2,3-g]quinoline (Description 14; 3.98g, 11.1mmol) and concentrated HCl (4.0ml) in ethanol (50ml) was hydrogenated over 10% palladium on charcoal at 50psi (344.8KPa) / room temperature for 30 hours. The mixture was filtered through celite and basified with solid K_2CO_3. Evaporation gave an off white solid which was dissloved in CH_2Cl_2 and the inorganics filtered off. Evaporation of the filtrate *in vacuo* afforded the title compound (D15) as a yellow solid (1.8g, 74%).

^{1}H NMR (250MHz,$CDCl_3$) δ (ppm): 8.46 (d, 1H), 7.72 (s, 1H), 6.96 (s, 1H), 6.77 (d, 1H), 4.14 (br s, 1H), 3.68 (t, 2H), 3.23 (t, 2H), 3.19 (br s, 4H), 2.68 (br s, 4H), 2.41 (s, 3H). MS: m/z = 269 (MH^+)

Description 16

5,7-Dichloro-3-methylbenzo[b]thiophene (D16)

This compound, MS: m/z MH^+ 217, was prepared from the appropriate thiophenol derivative as described in the following references:

1. N. B. Chapman, K. Clarke, and B. Iddon, J. Chem. Soc., 774, 1965.
2. N. B. Chapman, K. Clark, and N. Sawhney, J. Chem. Soc. (C), 2747, 1968.

Description 17

5-chloro-3,7-dimethylbenzo[b]thiophene (D17)

This compound, MS: m/z MH^+ 197, was prepared as described under Description 16.

Description 18

5-Chloro-3,7-dimethylbenzo[b]thiophene-2-sulphonyl chloride (D18)

To a solution of 5-chloro-3,7-dimethylbenzo[b]thiophene (D17) (1.5 g, 7.6 mmol) in chloroform at -10°C was added dropwise chlorosulphonic acid (1.3 ml, 19 mmol) and the resulting reaction mixture was stirred at -10°C for 2.5 hours and then at room temperature for 1 hour. The mixture was partitioned between dichloromethane and cold water (100 ml : 30 ml). The aqueous layer was extracted with dichloromethane (2 x 50 ml). The combined dichloromethane extracts were dried (Na_2SO_4), the solvent was removed to give the title compound (D18) as a tan solid (1.2 g, 53%). δ_H (250 MHz, $CDCl_3$-d_6), 2.56 (3H, s), 2.8 (3H, s), 7.38 (1H, s), 7.75 (1H, s).

Description 19

5,7-Dichloro-3-methylbenzo[b]thiophene-2-sulphonyl chloride (D19)

The compound was prepared according to the procedure described in Description 18. Yield: 87%. δ_H (250 MHz, $CDCl_3$-d_6), 2.8 (3H, s), 7.6 (1H, d, J = 1.6 Hz), 7.83 (1H, d, J = 1.6 Hz).

Description 20

7-Chloro-2-methylbenzo[b]thiophene (D20)

This compound, MS: M^+ 182, was prepared from the appropriate thiophenol derivative as described in the following reference:

W. K. Anderson, E. J. LaVoie, and J. C. Bottaro, J. Chem. Soc. Perkin I, 1, 1976.

Description 21

4,6-Dichloro-2-methyl-benzo[b]thiophene (D21)

This compound, MS: M^+ 216, was prepared as described under Description 20.

Description 22

7-Chloro-2-methylbenzo[b]thiophene-3-sulphonyl chloride (D22)

This compound was prepared from the corresponding benzo[b]thiophene (D20) in a similar way to that in Description 25. δ_H (250 MHz, $CDCl_3$-d_6), 2.97 (3H, s), 7.47 (2H, m,), 8.21 (1H, m). The compound was used without purification in the coupling step.

Description 23

4,6-Dichloro-2-methylbenzo[b]thiophene 3-sulphonyl chloride (D23)

The compound was prepared from the corresponding benzo[b]thiophene (D21) as described under Description 18. Yield 94%. δ_H (250 MHz, $CDCl_3$-d_6), 2.94 (3H, s), 7.59 (1H, d, $J = 1.7$), 7.69 (1H, d, $J = 1.7$).

Description 24

5-Chloro-3-methyl[b]benzofuran-2-sulphonyl chloride (D24)

To a solution of 5-chloro-3-methyl[b]benzofuran (T. Suzuki, T. Horaguchi, T. Shimizu, T. Abe, Bull. Chem. Soc. Jpn., 2762, 1983) (3.7g, 22 mmol) in diethyl ether (30 ml) at -70 °C under argon atmosphere was added dropwise 2.0 M solution of lithium diisopropylamide in hexane/tetrahydrofuran (15 ml). After stirring at this temperature for 30 minutes anhydrous sulphur dioxide was introduced over the surface of the reaction mixture for a period of one hour. The mixture was stirred for an additional hour at -70 °C, warmed to room temperature and diluted with diethyl ether (100 ml). The resulting tan precipitate was collected and dried in vacuo at room temperature to remove sulphur dioxide. This solid (2.8 g) was dissolved in dichloromethane (200 ml) and cooled to -50°C. N-Chlorosuccinimide (1.57g 11.8 mmol) in dichloromethane (10ml) was added dropwise over 10 minutes. The mixture was stirred for 3 hours at -50°C and one hour at room temperature. The solid was filtered off and washed with dichloromethane (200 ml). The combined filtrates were concentrated and the residue was purified by column chromatography on silica gel (eluting with hexane-dichloromethane (9 : 1, v/v) to give the title compound (D24) as an orange solid; (yield 24%). δ_H (250 MHz, $CDCl_3$), 2.61 (3H, s), 7.55 (1H, m), 7.68 (1H, m).

Description 25

5-Chloro-2-methylbenzo[b]thiophene-3-sulfonyl chloride (D25)

Sulfuryl chloride (0.75ml, 9.3mmol) was added to a stirred solution of DMF (0.85ml) at 0°C. After stirring at this temperature for 20 minutes a solution of 5-chloro-2-methylbenzo[b]thiophene (1.0g, 5.5mmol) in DMF (2ml) was added and the mixture was heated with stirring to 85°C for 2.5 hours. The cooled mixture was poured into cold water (100ml) and the mixture was extracted into ethyl acetate (100ml). The organic phase was dried and concentrated *in vacuo* to give the title compound (D25) as a crude yellow solid which was used without purification. δ_H (250 MHz, $CDCl_3$), 2.95 (3H, s), 7.45 (1H, m), 7.70 (1H, m), 8.30 (1H, m).

Description 26

4-(3,5-Dimethylpiperazin-1-yl)-6-nitroquinoline (D26)

The title compound (D26, yield 80%, MH^+ 287/288) was prepared from 4-chloro-6-nitroquinoline (D2) and 2,6-dimethylpiperazine in the same manner as described in Description 3.

Description 27

6-Amino-4-(3,5-dimethylpiperazin-1-yl)quinoline (D27)

The title compound (D27, yield 96%, MH+ 257/258) was prepared by hydrogenation of 4-(3,5-dimethylpiperazin-1-yl)-6-nitroquinoline (D26) as described in Description 4.

Description 28

4-(4-Methyl-piperazin-1-yl)-6-nitro-quinazoline (D28)

N-Methylpiperazine (13ml, 0.17mol) was added dropwise to a stirred solution of 4-chloro-6-nitroquinazoline (Yakugaku Zasshi, 1974, 94(4), 417-423) (2.44g, 11.6mmol) in dry dichloromethane (60ml). After stirring at room temperature for 18 hours, the mixture was washed with water (3 x 30ml) and the organic extract dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound (D28) as a solid (2.8g, 90%), δ_H (250 MHz, $CDCl_3$) 2.39 (3H, s), 2.64 (4H, t), 3.98 (4H, t), 7.96 (1H, d), 8.48 (1H, dd), 8.78 (1H, s), 8.97 (1H, d).

Description 29

6-Amino-4-(4-methyl-piperazin-1-yl)quinazoline (D29)

4-(4-Methyl-piperazin-1-yl)-6-nitro-quinazoline (D28) (3.18g, 11.6mmol) was hydrogenated as described in Description 4 to give the title compound (D29) (2.72g, 97%) as a solid MH^+ 244.

Description 30

5,7-Dichloro-2-methylbenzo[b]thiophene (D30)

This compound, MH^+ 217, was prepared as described in Description 16.

Description 31

5,7-Dichloro-2-methylbenzo[b]thiophene-3-sulphonyl chloride (D31)

This compound was prepared from 5,7-dichloro-2-methylbenzo[b]thiophene (D30) as described in Description 18.

Description 32

5-Chloro-3-ethyl-benzo[b]thiophene (D32)

This compound was prepared from 1-(4-chloro-phenylsulfanyl)-butan-2-one (Chim. Ther. 1973, **8**, 536-544) as described within Description 16; δ_H (250 MHz, $CDCl_3$), 1.36 (3H, t), 2.84 (2H, q), 7.13 (1H, s), 7.29 (1H, dd, J = 2, 8.5Hz), 7.70-7.76 (2H, m).

Description 33

5-Chloro-3-ethyl-benzo[b]thiophene-2-sulfonyl chloride (D33)

This compound was prepared from 5-chloro-3-ethyl-benzo[b]thiophene (D32) as described in Description 18; δ_H (250 MHz, $CDCl_3$), 1.39 (3H, t), 3.30 (2H, q), 7.54-7.91 (3H, m).

Description 34

5-Chloro-3-isopropyl-benzo[b]thiophene (D34)

This compound was prepared from 1-(4-chloro-phenylsulfanyl)-3-methyl-butan-2-one (Chim Ther. 1973, **8**, 536-544) as described within Description 16; δ_H (250 MHz, $CDCl_3$), 1.37 (6H, d), 3.22 (1H, quin), 7.27 (1H, dd, J = 2, 10.5Hz), 7.71-7.75 (2H, m).

Description 35

5-Chloro-3-isopropyl-benzo[b]thiophene-2-sulfonyl chloride (D35)

This compound was prepared from 5-chloro-3-isopropyl-benzo[b]thiophene (D34) as described in Description 18; δ_H (250 MHz, $CDCl_3$), 1.57 (6H, d), 4.26 (1H, quin), 7.52 (1H, dd, J = 1.9, 8.7Hz), 7.81 (1H, d J = 8.7Hz), 8.14 (1H, d, J = 1.8Hz).

Description 36

5-Bromo-3-methyl-benzo[b]thiophene-2-sulfonyl chloride (D36)

This compound was prepared from 5-bromo-3-methyl-benzo[b]thiophene (J. Het. Chem, 1988, **25**, 1271-1272) as described in Description 18; δ_H (250 MHz, $CDCl_3$), 2.81 (3H, s), 7.67-7.78 (2H, m), 8.05 (1H, d).

Description 37

2-Methyl-6-nitro-4-(piperazin-1-yl) quinoline (D37)

A stirred suspension of 4-choro-2-methyl-6-nitro quinoline (J. Amer. Chem Soc., 1964, **29**, 3548)(3.3g, 14.8mmol) and piperazine (5.1g, 59.1mmol) in toluene (30ml) were heated at reflux under argon for 24 hours. The reaction mixture was concentrated *in vacuo* and the residue was redissolved in dichloromethane (100ml) and the solution was washed with water (2 x 100ml). The organic phase was dried (Na2SO4) filtered and the filtrate was concentrated *in vacuo* to give the title compound (D37) as a solid (3.8g, 95%), MS, MH^+ 273.

Description 38

4-(4-*tert*-Butoxycarbonylpiperazin-1-yl)-2-methyl –6-nitroquinoline (D38)

Water (50ml) was slowly added to a stirred solution of 2-methyl-6-nitro-4-(piperazin-1-yl) quinoline (D37) (3.8g, 14mmol) in tetrahydrofuran (THF)(50ml) followed by a solution of di-tert-butyldicarbonate (3.06g, 14mmol) in THF (13ml) over 10 minutes. Potassium carbonate (2.03g, 14.7mmol) was added in portions and the reaction mixture was left to stir at room temperature for 60 hours. The reaction mixture was concentrated *in vacuo* to remove THF and the resulting aqueous mixture was extracted with dichloromethane (2 x 100ml). The combined organic phases were washed with water (2 x 100ml), dried (Na2SO4) and concentrated *in vacuo* to a foam which was stirred with a mixture of diethyl ether/hexane (1:1)(100ml) to give the title compound (D38) as an insoluble solid (4.6g, 88%), M.S. MH^+ 373.

Description 39

6-Amino-4-(4-*tert*-butoxycarbonylpiperazin-1-yl)-2-methyl quinoline (D39)

The title compound (D39), MS: MH^+ 343, was prepared from 4-(4-*tert*-butoxycarbonylpiperazin-1-yl)-2-methyl –6-nitroquinoline (D38) as described in Description 4, using a mixture of ethanol/dioxan (1:1) as solvent.

Description 40

3-Methyl-6-nitro-4-(piperazin-1-yl) quinoline (D40)

The title compound (D40), MS: MH^+ 273, was prepared in 54% yield from 4-chloro-3-methyl-6-nitro quinoline (J. Chem. Soc., 1950, 2092, 2094) as described in Description 37.

Description 41

4-(4-*tert*-Butoxycarbonylpiperazin-1-yl)-3-methyl –6-nitroquinoline (D41)

The title compound (D41), M.S. MH^+ 373, was prepared in 98% yield from 3-methyl-6-nitro-4-(piperazin-1-yl) quinoline (D40) as described in Description 38.

Description 42

6-Amino-4-(4-*tert*-butoxycarbonylpiperazin-1-yl)-3-methyl quinoline (D42)

The title compound (D42), M.S. MH^+ 343, was prepared in 98% yield from 4-(4-*tert*-butoxycarbonylpiperazin-1-yl)-3-methyl –6-nitroquinoline (D41) as described in Description 39.

Description 43

4-(S-Hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-6-nitro quinoline (D43)

A suspension of 4-chloro-6-nitroquinoline (D2)(860mg, 4.1mmol) and (S)-octahydro-pyrrolo[1,2-a]pyrazine (571mg, 4.5mmol)(J. Med. Chem., 1993, **36**, 2311-2320) in toluene (18ml) was heated under argon at reflux for 40 hours. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography on silica

gel eluting with a gradient of dichloromethane/methanol to give the title compound (D43) as a foam (315mg, 26%), M.S. MH^+ 299.

Description 44

6-Amino-4-(S-hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-quinoline (D44)

The title compound (D44), M.S., MH^+ 269, was prepared from 4-(S-hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-6-nitro quinoline (D43) as described in Description 4.

Description 45

4-((S)-3-Methyl-piperazin-1-yl)-6-nitroquinoline (D45)

The title compound (D45, MH^+ 273/274, yield 98%) was prepared as described under Description 5.

Description 46

4-(4-*tert*-Butoxycarbonyl-((S)-3-methyl-piperazin-1-yl)-6-nitroquinoline (D46)

The title compound (D46, MH^+ 373/374, yield 99%) was prepared in a similar way as described under Description 6.

Description 47

6-Amino-4-(4-*tert*-butoxycarbonyl-((S)-3-methyl-piperazin-1-yl)quinoline (D47)

4-(4-*tert*-Butoxycarbonyl-(S)-methyl-piperazin-1-yl)-6-nitroquinoline (D46) was hydrogenated as described in Description 4 to give the title compound (D47) in 11% yield, MH^+ 343/344.

Description 48

4-((R)-3-Methyl-piperazin-1-yl)-6-nitroquinoline (D48)

The title compound (D48, MH^+ 273/274, yield 73%) was prepared as described under Description 5.

Description 49

4-(4-*tert*-Butoxycarbonyl-(R)-3-methyl-piperazin-1-yl)-6-nitroquinoline (D49)

The title compound (D49, MH^+ 373/374 , yield 99%) was prepared in a similar way as described under Description 6.

Description 50

6-Amino-4-(4-*tert*-butoxycarbonyl-((R)-3-methyl-piperazin-1-yl)quinoline (D50)

4-(4-*tert*-Butoxycarbonyl-(R)-methyl-piperazin-1-yl)-6-nitroquinoline (D49) was hydrogenated as described in Description 4 to give the title compound (D50) in 45% yield, MH^+ 343/344.

Description 51

4-(*trans*-2,5-Dimethyl-piperazine-1-yl)- 6-nitroquinoline (D51)

A mixture of *trans* 2,5-dimethylpiperazine (0.12 g, 1.06 mmol), 4-chloro-6-nitroquinoline (D2) (0.1 g, 0.48 mmol) and potassium fluoride (42 mg, 0.72 mmol) in 1-methyl-2-pyrrolidinone (7 ml) was stirred at 120 oC under argon for 24 hours. The solvent was removed and the residue was co-evaporated with toluene (1x10ml). The product was purified by column chromatography on silica gel eluting with dichloromethane-methanol gradient to give the title compound (D51) as a tan oil (50 mg, 36%), MH+ 287/288.

Description 52

4-(4-*tert*-Butoxycarbonyl-*trans*-2,5-dimethyl-piperazin-1-yl)-6-nitroquinoline (D52)

The title compound (D52, MH+ 387/388 , yield 99%) was prepared in a similar way as described under Description 6.

Description 53

6-Amino-4-(4-*tert*-butoxycarbonyl-*trans*-2,5-dimethyl-piperazin-1-yl)quinoline (D53)

A mixture of 4-(4-*tert*-butoxycarbonyl-*trans*-2,5-dimethyl-piperazin-1-yl)-6-nitroquinoline (D52) (0.32 g) and iron (0.23 g) in saturated aqueous ammonium chloride (15 ml) and methanol (10 ml) was heated at reflux for 2.5 hours. The cooled mixture was filtered through Celite (Diatomaceous Earth), the Celite was washed with methanol (6x10 ml) and the combined filtrates were evaporated to a small volume. The product was then extracted with dichloromethane (5x3 0 ml), the combined extracts were dried (Na2SO4), and the solvent was removed. The product was purified by column chromatography on silica gel eluting with dichloromethane-ethyl acetate/dichloromethane-methanol gradient to give the title compound (D53) as a tan solid (0.23 g, 77%), MH+ 357/358.

Description 54

(R)-3-Isopropyl –piperazine (D54)

A mixture of (R)-3-isopropyl-2,5-piperazinedione (2.5 g, 16 mmol) and borane-tetrahydrofuran complex (1M solution in tetrahydrofuran, 64 ml) in tetrahydrofurane (50 ml) was heated at reflux under argon for 24 hours. The solvent was removed, the residue was dissolved in tetrahydrofuran-6M aqueous hydrochloride solution (100ml:40 ml) and it was then heated at reflux for 5 hours. On cooling, the mixture was concetrated to a small volume, diluted with water (200 ml), basified with 40% aqueous NaOH and extracted with dichloromethane (3x100 ml). The organic extracts were dried (Na2SO4), the solvent was removed to give a pale oil which was treated diethyl ether (200ml) at 5 oC to afford the title compound as a colourless solid (D54) (0.4 g, 19%). MH+129/130.

Description 55

4-((R)-3-isopropyl-piperazin-1-yl)-6-nitroquinoline (D55)

The title compound (D55, MH+ 301/302, yield 43%) was prepared as described under Description 51.

Description 56

4-(4-*tert*-Butoxycarbonyl-(R)-3-isopropyl-piperazin-1-yl)-6-nitroquinoline (D56)

The title compound (D56, MH+ 402/403, yield 90%) was prepared in a similar way as described under Description 6.

Description 57

6-Amino-4-(4-*tert*-butoxycarbonyl-(R)-3-isopropyl-piperazin-1-yl)quinoline (D57)

The title compound (D57) MH+ 371/372, yield 54%) was prepared as described under Description 53.

Example 1

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-[4-methylpiperazin-1-yl]-quinolin-6-yl)-amide hydrochloride (E1)

A solution of 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl chloride (115mg, 0.41mmol) and 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D4) (100mg, 0.41mmol) in dichloromethane (5ml) was stirred for 24 hours under argon. The precipitated solid was filtered and re-crystallised from ethanol/diethyl ether to give the title compound (E1) as a white solid (163mg, 76%), MH^+ -HCl 487/489.

The following hydrochloride compounds (E2-E6) (Table 1) were prepared as described in Example 1 by reaction of the appropriate sulfonyl chloride derivative with 6-amino-4-(4-methylpiperazin-1-yl)quinoline (D4) or the appropriate quinoline. The compound of Example 5 was purified by column chromatography on silica gel, eluting with dichloromethane-methanol gradient. The aminoquinoline used to prepare the compound of Example 5 was prepared as described in Descriptions 26 and 27. The aminoquinoline used to prepare the compound of Example 6 was prepared as described in Descriptions 28 and 29.

Table 1

Compound	MS MH^+
5-Chloro-naphthalene-2-sulfonic acid (4-[4-methyl-piperazin-1-yl]-quinolin-6-yl)-amide (E2)	467/469

4-Bromo-*N*-[4-(4-methyl-piperazin-1-yl)-quinolin-6-yl]-benzenesulfonamide (E3)	461/463
3,5-Dichloro-*N*-[4-(4-methyl-piperazin-1-yl)-quinolin-6-yl]-benzenesulfonamide (E4)	451/453
5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-[3,5-dimethylpiperazin-1-yl]-quinolin-6-yl)-amide (E5)	501/503
5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid [4-(4-methyl-piperazin-6-yl]-quinazolin-6-yl)amide (E6)	488/490

Example 7

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)-amide hydrochloride (E7)

A solution of 5-chloro-3-methyl-benzo[b]thiophen-2-sulfonyl chloride (285mg, 1.0mmol), 6-amino-4-(4- *tert*-butoxycarbonylpiperazin-1-yl)quinoline (D7) (300mg, 0.92mmol) and pyridine (0.15ml, 1.8mmol) in dichloromethane (5ml) was stirred for 24 hours under argon. The solution was washed with 1M hydrochloric acid (5ml) then water (5ml), dried (Na_2SO_4) and concentrated *in vacuo* to a residue. The residue was dissolved in tetrahydrofuran (5ml) and concentrated hydrochloric acid (1ml) and the solution heated at reflux for 1.5 hours. The solution was concentrated and the residue was stirred with acetone to give the title compound (E7) as a white solid (182mg, 39%) MH^+ -HCl 473/475.

The following hydrochloride compounds (E8-E26) (Table 2) were prepared as described in Example 7 by reaction of the appropriate sulfonyl chloride derivative with 6-amino-4-(4- *tert*-butoxycarbonylpiperazin-1-yl)quinoline (D7). The sulfonyl chloride used in the preparation of Example 9 is described in Description 24. Other sulfonyl chlorides are prepared as indicated: Example 10 (D16 and D19), E13 (D25), E15 (D17 and D18), E16 (D20 and D22), E17 (D21 and D23), E18 (D30 and D31), E21 (D36), E24 (D32 and D33), E25 (D34 and D35).

Table 2

Compound	MS MH^+
3,5-Dichloro-*N*-(4-piperazin-1-yl-quinolin-6-yl)-benzenesulfonamide (E8)	437/439
5-Chloro-3-methyl-benzofuran-2-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)amide (E9)	457/459
5,7-Dichloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-piperazin-1-	507/509

yl-quinolin-6-yl)-amide (E10)	
5-Chloro-naphthalene-2-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)-amide (E11)	453/455
5-Chloro-naphthalene-1-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)-amide (E12)	451/453
5-Chloro-2-methyl-benzo[b]thiophene-3-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)-amide (E13)	473/475
2-Dibenzofuran-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)-amide (E14)	459
5-Chloro-3,7-dimethyl-benzo[b]thiophene-2-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)-amide (E15)	487/489
7-Chloro-2-methyl-benzo[b]thiophene-3-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)-amide (E16)	473/475
4,6-Dichloro-2-methyl-benzo[b]thiophene-3-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)-amide (E17)	507/509
5,7-Dichloro-2-methyl-benzo[b]thiophene-3-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)-amide (E18)	507/509
Biphenyl-4-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)-amide (E19)	445
4-*tert*-Butyl-*N*-(4-piperazin-1-yl-quinolin-6-yl)-benzenesulfonamide (E20)	425
5-Bromo-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)-amide (E21)	517/519
4-*n*-Butyl-*N*-(4-piperazin-1-yl-quinolin-6-yl)-benzenesulfonamide (E22)	425
4-Chloro-2,5-dimethyl-*N*-(4-piperazin-1-yl-quinolin-6-yl)-benzenesulfonamide (E23)	431/433
5-Chloro-3-ethyl-benzo[b]thiophene-2-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)-amide (E24)	487/489
5-Chloro-3-isopropyl-benzo[b]thiophene-2-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)-amide (E25)	501/503
4-Iodo-*N*-(4-piperazin-1-yl-quinolin-6-yl)-benzenesulfonamide (E26)	495

Example 27

1-(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-8-(4-methyl-piperazin-1-yl)-2,3-dihydro-1H-pyrrolo[2,3-g]quinoline Hydrochloride (E27)

A solution of 5-chloro-3-methyl-benzothiophene-2-sulfonyl chloride (75mg, 0.27mmol) and 8-(4-methyl-piperazin-1-yl)-2,3-dihydro-1H-pyrrolo[2,3-g]quinoline (D17)(72mg, 0.27mmol) in 1,2-dichloroethane was refluxed for 5 hours under argon. The cooled reaction mixture was washed with 0.1M potassium hydroxide solution, dried (Na_2SO_4) and concentrated to a solid which was purified by column chromatography over silica gel

eluting with methanol/dichloromethane (1:9) to yield a solid which was treated with 1M ethereal hydrogen chloride to afford the title compound (E27) (80mg, 54%), MH^+ 513/515.

The following hydrochloride compounds (E28-E30)(Table 3) were prepared as described in Example 7 by reaction of the appropriate sulfonyl chloride derivative with 6-amino-4-(4-*tert*-butoxycarbonylpiperazin-1-yl)-2-methyl quinoline (D39).

Table 3

Compound	MS MH^+
5-Chloro-naphthalene-2-sulfonic acid (2-methyl-4-piperazin-1-yl-quinolin-6-yl) amide (E28)	467/469
5-Chloro-3-methyl-benzo[b]thiophen-2-sulfonic acid (2-methyl-4-piperazin-1-yl-quinolin-6-yl) amide (E29)	487/489
5-Chloro-3-methyl-benzofuran-2-sulfonic acid (2-methyl-4-piperazin-1-yl-quinolin-6-yl) amide (E30)	471/473

The following hydrochloride compounds (E31-E34)(Table 4) were prepared as described in Example 7 by reaction of the appropriate sulfonyl chloride derivative with 6-amino-4-(4-*tert*-butoxycarbonylpiperazin-1-yl)-3-methyl quinoline (D42). The sulfonyl chloride used to prepare Example 33 is described in Descriptions D19 and D16.

Table 4

Compound	MS MH^+
5-Chloro-naphthalene-2-sulfonic acid (3-methyl-4-piperazin-1-yl-quinolin-6-yl) amide (E31)	467/469
5-Chloro-3-methyl-benzo[b]thiophen-2-sulfonic acid (3-methyl-4-piperazin-1-yl-quinolin-6-yl) amide (E32)	487/489
5,7-Dichloro-3-methyl-benzo[b]thiophen-2-sulfonic acid (3-methyl-4-piperazin-1-yl-quinolin-6-yl) amide (E33)	521/523
5-Chloro-3-methyl-benzofuran-2-sulfonic acid (3-methyl-4-piperazin-1-yl-quinolin-6-yl) amide (E34)	471/473

Example 35

4-*tert*-Butyl-*N*-[4-(S-hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-quinolin-6-yl-benzene sulfonamide hydrochloride (E35)

4-*tert*-Butyl-benzene sulfonyl chloride (112mg, 0.48mmol) was added to a solution of 6-amino-4-(S-hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-quinoline (D44)(117mg, 0.44mmol) in dry dichloromethane (5ml) at room temperature and the solution was left to stir for 24 hours. The reaction mixture was concentrated *in vacuo* and purified by column chromatography on silica gel eluting with a gradient of dichloromethane/methanol to afford the title compound (E35) (39mg, 19%), MS: MH^+ 465.

The hydrochloride compounds (E36, E37)(Table 5) were prepared as described in Example 35 by reaction between the appropriate sulfonyl chloride and quinoline derivatives. The hydrochloride compounds (E38-E41) were prepared as described in Example 7 and when appropriate the compounds were purified by column chromatography. The descriptions of the preparations of the quinoline derivatives used to derive these examples are indicated as follows: E36 (D44), E37 (D27), E38 (D47), E39 (D50), E40 (D57), E41 (D53).

Table 5

Compound	MS MH^+
5-Chloro-3-methyl-benzo[b]thiophen-2-sulfonic acid [4-(S-hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-quinolin-6-yl] amide (E36)	513/515
5-Chloro-2-methyl-benzo[b]thiophene-3-sulfonic acid (4-[3,5-dimethylpiperazin-1-yl]-quinolin-6-yl)-amide (E37)	501/503
5-Chloro-3-methyl-benzo[b]thiophene-2-sulphonic acid [4-((S)-3-methyl-piperazine-1yl)-quinolin-6-yl]-amide (E38)	487/489
5-Chloro-3-methyl-benzo[b]thiophene-2-sulphonic acid [4-((R)-3-methyl-piperazine-1-yl)-quinolin-6-yl]-amide (E39)	487/489
5-Chloro-3-methyl-benzo[b]thiophene-2-sulphonic acid [4-((R)-3-isopropyl-piperazine-1-yl)-quinolin-6-yl]-amide (E40)	515/517
5-Chloro-3-methyl-benzo[b]thiophene-2-sulphonic acid [4-(*trans*-2,5-di-methyl-piperazine-1-yl)-quinolin-6-yl]-amide (E41)	501/503

Example 42

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid [8-(4-methyl-piperazin-1-yl)-naphthalen-2-yl]-amide hydrochloride (E42)

A solution of 2-amino-8-(4-methyl-piperazin-1-yl)-naphthalene (EP 701819)(68mg, 0.28mmol) in dry dichloromethane (3ml) was added to 5-chloro-3-methyl-

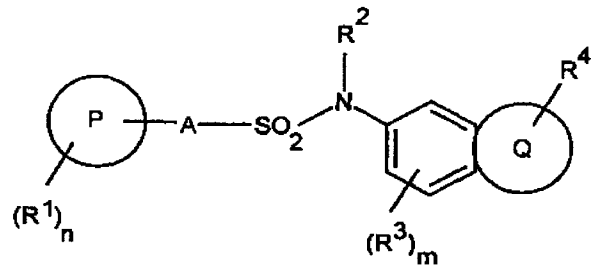
benzo[b]thiophen-2-sulfonyl chloride (87mg, 0.31mmol) and the solution was left to stir for 24 hours. The precipitated solid was collected and purified by column chromatography on silica gel eluting with a gradient of ethyl acetate/ethanol/water to afford the title compound (E42, 58mg, 40%), MS: MH^+ 486/488.

Pharmacological data

Compounds can be tested following the procedures outlined in WO 98/27081.
All compounds tested showed good affinity for the 5-HT_6 receptor, having pKi values in the range 7.1 – 9.5 at human cloned 5-HT_6 receptors.

Claims:

1. A compound of formula (I) or a salt thereof:



(I)

wherein
P is phenyl, naphthyl, a 5 or 6 membered heteroaryl ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, or a bicyclic or tricyclic heteroaryl ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur;
A is a single bond, a C_{1-6}alkylene or a C_{2-6}alkenylene group;
R^1 is halogen, C_{1-6}alkyl optionally substituted by one or more halogen atoms, C_{3-6}cycloalkyl, phenyl, COC_{1-6}alkyl, C_{1-6}alkoxy, OCF_3, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, nitro, amino, C_{1-6}alkylamino or diC_{1-6}alkylamino;
n is 0, 1, 2, 3, 4 or 5;
R^2 is hydrogen, C_{1-6}alkyl or together with a group R^3 forms a group -$(CR^6R^7)_p$- where R^6 and R^7 are independently hydrogen or C_{1-6}alkyl and p is 2, 3 or 4;
R^3 is C_{1-6}alkyl optionally substituted by one or more halogen atoms, halogen, C_{1-6}alkoxy or together with the group R^2 forms a group -$(CR^6R^7)_p$- as defined above;
m is 0, 1 or 2;
R^4 is a group -X-R^5 where X is a single bond, CH_2, O, NH or N-C_{1-6}alkyl and R^5 is an optionally substituted 5- to 7-membered heterocyclic ring or a bicyclic heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen;
Q is a phenyl ring or is a 6 membered heteroaryl ring containing one or two nitrogen atoms.

2. A compound according to claim 1 in which P is phenyl, naphthyl, benzofuryl or benzothienyl.

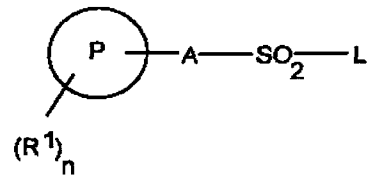
3. A compound according to claims 1 or 2 in which R^1 is halogen or a C_{1-6}alkyl group optionally substituted by one or more halogen atoms.

4. A compound according to any one of claims 1 to 3 in which R^4 is a piperazine ring optionally substituted by C_{1-6}alkyl.

5. A compound according to any one of claims 1 to 4 in which Q together with the phenyl group to which it is fused forms a quinoline, isoquinoline or quinazoline ring.

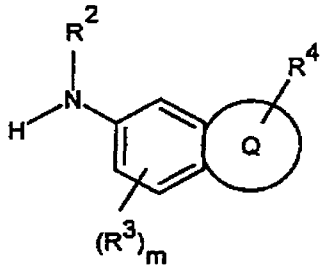
6. A compound according to claim 1 which is selected from Examples E1 - E42 or a pharmaceutically acceptable salt thereof.

7. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises the coupling of a compound of formula (II) or a protected derivatives thereof:



(II)

in which R^1, n, P and A are as defined in formula (I) and L is a leaving group with a compound of formula (III) or a protected derivatives thereof:



(III)

in which Q, m, R^2, R^3 and R^4 are as defined in formula (I) and optionally thereafter:

- removing any protecting groups,
- forming a pharmaceutically acceptable salt.

8. A compound according to any one of claims 1 to 6 for use in therapy.

9. A compound according to any one of claims 1 to 6 for use in the treatment of anxiety, depression, cognitive memory disorders, schizophrenia or ADHD.

10. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 6 and a pharmaceutically acceptable carrier or excipient.